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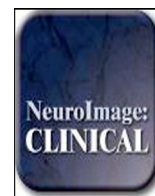


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Functional and structural brain correlates of risk for major depression in children with familial depression



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ABSTRACT

Despite growing evidence for atypical amygdala function and structure in major depression, it remains uncertain as to whether these brain differences reflect the clinical state of depression or neurobiological traits that predispose individuals to major depression. We examined function and structure of the amygdala and associated areas in a group of unaffected children of depressed parents (at-risk group) and a group of children of parents without a history of major depression (control group). Compared to the control group, the at-risk group showed increased activation to fearful relative to neutral facial expressions in the amygdala and multiple cortical regions, and decreased activation to happy relative to neutral facial expressions in the anterior cingulate cortex and supramarginal gyrus. At-risk children also exhibited reduced amygdala volume. The extensive hyperactivation to negative facial expressions and hypoactivation to positive facial expressions in at-risk children are consistent with behavioral evidence that risk for major depression involves a bias to attend to negative information. These functional and structural brain differences between at-risk children and controls suggest that there are trait neurobiological underpinnings of risk for major depression.

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1. Introduction

Neuroimaging studies have shown that patients with major depression display differences in the function and structure of brain regions involved in emotion identification and reactivity, including the amygdala, hippocampus, striatum, and orbitofrontal cortex, as well as areas involved in emotional regulation, such as dorsolateral prefrontal cortex and anterior cingulate cortex (Stuhrmann et al., 2011). It is unclear, however, whether these differences reflect the clinical state of major depression or neurobiological traits that predispose individuals to be at risk for major depression. Such neurobiological traits are important to identify because they could serve as neural biomarkers of risk for major depression in children and could improve the identification of a subgroup of children at very high risk for major depression that could

be targeted for early intervention. One approach to identifying such neurobiological traits is to examine brain function and structure in children who are not themselves depressed but are at familial risk for major depression by virtue of having a parent with a history of major depression, which increases the risk of major depression by three to five fold (Williamson et al., 2004). Here, we compared brain function and structure between children ages 8–14 with versus without familial risk for major depression.

Perhaps the most consistent functional brain difference in acute adult major depression has been hyperactivation of the amygdala to faces with fearful (Peluso et al., 2009; Sheline et al., 2001; Zhong et al., 2011) or sad (Fu et al., 2004; Surguladze et al., 2005; Suslow et al., 2010; Victor et al., 2010) expressions. In contrast, depressed adults often exhibit hypoactivation for happy facial expressions in variable regions including anterior cingulate cortex, amygdala, and fusiform gyrus (Surguladze et al., 2005; Suslow et al., 2010; Victor et al., 2010), although hyperactivation has also been reported (Gotlib et al., 2005; Keedwell et al., 2005). Increased activation to emotional faces has also been found in adolescents (Roberson-Nay et al., 2006; Yang et al., 2010) and 4–6 year olds (Gaffrey et al., 2013) with major depression.

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One approach to distinguishing the clinical state of major depression from predisposing neurobiological traits has been to examine remitted patients who had major depression but who are not currently depressed, but this approach has yielded mixed findings. A number of studies reported that remitted patients (usually treated with antidepressants) do not exhibit amygdala hyperactivation to negative facial expressions (Fu et al., 2004; Norbury et al., 2010; Sheline et al., 2001; Thomas et al., 2011; Victor et al., 2010), suggesting that amygdala hyperactivation is associated with the state and not the trait of major depression. Other evidence, however, favors the idea that amygdala hyperactivation is associated with trait predisposition to major depression. First, two studies of unmedicated patients with remitted major depression found amygdala hyperactivation to emotional faces that did not differ from patients in acute episodes (Neumeister et al., 2006; Victor et al., 2010). Second, healthy individuals with clinical traits thought to predispose for major depression, such as high neuroticism or pessimistic cognitions, also showed increased amygdala responses to emotional faces (Chan et al., 2009; Zhong et al., 2011). However, the complexity of variable histories of major depression and treatment for major depression may make it difficult to distinguish state versus trait characteristics of major depression in patients with a history of major depression.

Several studies have examined children or adolescents with familial risk for major depression but without depression themselves. One study using this approach focused on the amygdala and nucleus accumbens as regions of interest (ROIs), and found that subjects (10–18 years of age) at familial risk for major depression exhibited amygdala hyperactivation to fearful facial expressions and nucleus accumbens hypoactivation to happy facial expressions relative to subjects without familial risk for major depression (Monk et al., 2008). Another study of older adolescents, however, found no differences in amygdala activation between those with or without family history of major depression (although those at risk adolescents had reduced dorsolateral prefrontal cortex responses to emotional faces) (Mannie et al., 2011).

In addition to functional abnormalities, volumetric abnormality in amygdala structure (volume) has been found in studies of major depression, although the findings have been inconsistent (Frodl et al., 2003; Hastings et al., 2004; MacMaster et al., 2008). A meta-analysis suggested that these inconsistencies may be attributed to differences in medication status (Hamilton et al., 2008). Unmedicated patients tend to have smaller amygdala volumes, whereas medicated patients tend to have larger amygdala volumes compared to controls. However, as with functional differences in depressed patients, it remains unclear whether smaller amygdala volume represents a state or trait correlate of major depression. Resolving the contradictory findings in the neuroimaging literature as to whether functional and structural brain findings reflect state or trait neurobiological underpinnings of major depression has important clinical and scientific implications. If they were to be found to represent neurobiological underpinnings of risk for major depression, they may help identify children at very high risk for major depression who may be targeted for prevention or early intervention to avoid developing a serious illness such as major depression.

In the present study, we compared neuroimaging findings in children at familial risk for major depression who were offspring of parents with well-characterized major depressive disorder (at-risk group) with age-matched children who were offspring of parents who had no lifetime history of any mood disorder (control group). We performed whole-brain voxel-wise fMRI analyses, and focused additional *a priori* analyses on the amygdala, a limbic area that often had shown differences in neuroimaging studies of major depression. The children, while being scanned, viewed fearful (negative) and happy (positive) facial expressions, and also neutral facial expressions as a baseline. Given the behavioral attention bias towards negative facial expression in at-risk children and bias towards positive facial expression in controls (Gibb et al., 2009; Joormann et al., 2007; Kujawa et al., 2011), we hypothesized that at-risk children would show greater brain responses

to negative-valenced emotional faces, and lesser brain responses to happy faces compared to control children.

2. Methods

2.1. Participants

Thirty-eight offspring ages 8–14 years of parents with lifetime history of unipolar depression (at-risk group) and 23 age-matched offspring of parents with no lifetime mood disorder (control group) participated in the study. Eligible participants were right-handed, had normal or corrected-to-normal visual acuity, had average or higher IQ ($IQ > 90$) and had a working command of the English language. Exclusion criteria included the presence of acute psychosis or suicidality in a parent or a child; the presence at any point in the lifespan of bipolar disorder in the parent, autism in the child, or a lifetime history of a traumatic brain injury or neurological disorder in the child. Children were also excluded if they had conditions incompatible with MRI (e.g., metal implants, braces, electronically, magnetically, or mechanically activated devices such as cochlear implants, or claustrophobia). Children were not excluded on the basis of personal history of major depression but could not have current major depressive disorder or dysthymia.

2.1.1. Recruitment

Participants were recruited from among participants in longitudinal studies of offspring at risk, conducted in the Clinical and Research Program in Pediatric Psychopharmacology at the Massachusetts General Hospital, supplemented with participants responding to advertisements to the community. The sample included 43 children from a study of offspring at risk for major depression and/or ADHD or neither disorder (31 at-risk and 12 controls); 3 children from a study of offspring at risk for major depression and/or panic disorder or neither disorder (2 at-risk and 1 control); and 6 control offspring of parents without mood disorders from a study comparing offspring of parents with and without bipolar disorder. Children from each of these studies had been recruited when the children were preschool-age from advertisements to clinical psychiatry departments and to the community calling either for adults who had been treated for depression and who had preschool-age children or for families in which neither parent had been treated for mood disorder (see e.g., Rosenbaum et al., 2000). Both parents in each family had been assessed in the course of these studies using the Structured Interview for DSM-IV (First et al., 1995). The sample was supplemented with 5 additional children at-risk, one of whom was a child from a study of siblings of children with bipolar disorder who was found on parental interview to have a parent with unipolar depression, and 4 of whom answered community advertisements for controls but were found to have a parent with major depression. Four additional control children were enrolled based on advertisements to the community calling for children in the age-range 8–14 whose parents had never been treated for depression.

Each of the prior studies from which we recruited had been approved by the Institutional Review Board at the Massachusetts General Hospital, and the present study was approved by the Institutional Review Boards at the Massachusetts General Hospital and at the Massachusetts Institute of Technology. Parents provided written informed consent for their and their child's participation, and youths provided written assent.

2.1.2. Diagnostic assessment

At enrollment for the present study, each child and both parents in each family were assessed for current and lifetime mood disorders (major depression, bipolar disorder, and dysthymia) in the interval since they had last been interviewed (or, for those recruited anew from the community, across their lifetime), using structured clinical interviews in which the mother was the informant. Interviews about

parents used the depression, mania, dysthymia modules, and psychosis modules from the Structured Interview for DSM-IV (First et al., 1995) and those about the child used the depression, mania, dysthymia, and psychosis modules from the Schedule of Affective Disorders and Schizophrenia for School-Aged Children—Epidemiological Version (KSADS-E) for DSM-IV (Orvaschel, 1994).

2.1.3. Other assessments

2.1.3.1. Cognitive function. To compare cognitive function across groups, we used the Kaufman Brief Intelligence Test-2 (KBIT-2), a 20-minute screen for verbal and nonverbal cognitive functioning (Kaufman and Kaufman, 2004).

2.1.3.2. Current symptoms, parent report. To assess current behavioral and emotional symptoms in the children, we asked mothers to complete the Child Behavior Checklist (CBCL) (Achenbach and Rescorla, 2001) about their child. The CBCL records, in standardized format, behavioral problems and competencies of children ages 6–18 years. Normed on a nationally representative sample of 1753 youths, it includes a total problems score, as well as scores reflecting internalizing (affective and anxiety) and externalizing symptoms (attentional problems and disruptive behavior). *T*-scores of 70 and above have been shown to clearly discriminate clinical-range from non-clinical range children. The CBCL also includes a subscale measuring specific symptoms relevant to major depression, the affective problems scale.

In addition, because emotional dysregulation may place children at risk for major depression, we also administered the Emotion Regulation Checklist (ERC) (Shields and Cicchetti, 1998, 1997). This 24-item parent-report measure assesses children's emotional regulation capturing aspects like emotional lability, intensity, valence, flexibility, and appropriateness to situation. In school-age children (through age 12) it yields two factors, Lability/Negativity (mood swings, reactive anger, emotional intensity and dysregulated positive emotions) and Emotion Regulation (understanding emotions, equanimity, and empathy).

2.1.3.3. Current symptoms, self-report. To assess current depressive symptoms by self-report, we administered the Child Depression Inventory (CDI) (Kovacs, 1985) to all children. This is a 27-item self-report questionnaire that measures total depression, and five factors: negative mood, interpersonal problems, ineffectiveness, anhedonia, and negative self esteem. Because this was a non-clinical sample including young children, we omitted the item asking about suicidal ideation.

2.1.4. Final participants included in analysis

Two participants from the at-risk group and 8 participants from the control group were excluded from the functional analysis due to excessive head movement during the functional scan (greater than 3 mm displacement in *x*, *y* or *z* direction). One additional control participant was excluded due to chance-level task performance in the face-match task. The final functional analysis included 36 at-risk and 14 control participants. Structural analysis included 37 at-risk and 18 control participants after excluding participants with substantial movement during the structural scan that resulted in poor structural image quality.

The final sample of 36 at-risk children included for functional analysis consisted of 32 children with no current or prior symptoms for depression (33 of the 37 at-risk children included in the structural analysis had no previous or current depression symptoms), two children with previous history of major depression that had remitted, and two children with current clinical-range CBCL internalizing scores. To determine if our results were driven by participants with past or current symptoms for depression, we performed two additional analyses: 1) we repeated the between-group whole-brain fMRI analysis after excluding the two participant with previous depression and the two participants with clinical-level CBCL internalizing scores; and 2) we repeated the

between-group whole-brain fMRI analysis after including total CBCL scores as a covariate, since the average total CBCL score differed between the at-risk and control groups.

2.2. Face-match task

Participants completed a simple perceptual matching task, adapted from Hariri et al. (2005), during fMRI scanning. Participants viewed a trio of images on the screen and were asked to select one of the two images on the bottom that was identical to the target image (on the top). There were four different types of stimuli: fearful faces, happy faces, neutral faces, and objects. There were 2 runs, with 2 blocks of each type of stimulus per run. Each block consisted of 6 trials, each presented for 3 s. Each run lasted 3 min and 18 s (99 TR). Block order was counterbalanced across participants. Face stimuli were taken from Radboud and NimStim stimulus sets (Langner et al., 2010; Tottenham et al., 2009). Face stimuli were presented via 72 unique actors (36 from each set, half male, half female from each set). Each actor presented a happy, neutral, and fearful expression, for a total of 216 unique face stimuli. All actors were facing directly forward and images were cropped to contain only the actors' heads. Each actor was seen once with a randomly selected expression. Twenty-four unique object stimuli consisting of fruits and vegetables were used in the study. Each object was seen once per scan. Stimulus sequence was randomized within each block for every run. Left and right responses were counterbalanced across conditions.

2.3. Imaging procedure

Data were acquired on a 3 T TrioTim Siemens scanner using a 32-channel head coil. T1-weighted whole-brain anatomical images (MPRAGE sequence, 256 × 256 voxels, 1 × 1.3-mm in-plane resolution, 1.3-mm slice thickness) were acquired. Functional MRI images were obtained in 3-mm-thick transverse slices, covering the entire brain (interleaved EPI sequence, repetition time = 2 s, 3 × 3 × 3 mm voxels). Online prospective acquisition correction (PACE) was applied to the EPI sequence. PACE tracks the head of the subject and updates the position of the field-of-view and slice alignment during acquisition. The parameters for each time point are updated based on motion correction parameters calculated from the previous two time points. Two dummy scans were included at the start of the sequence.

2.4. Mock scan session

Before the MRI scanning session, all participants completed a mock-scanner training session where they practiced lying still in a mock scanner. Participants watched a cartoon movie of their choice in the mock scanner while their head motion was monitored by a motion detector. The movie would be temporarily shut off if their head moved more than 3 mm. Recordings of the actual scanner sounds were played in the mock scanner during the training. The mock scan session lasted about 30 min for each child.

2.5. fMRI analysis

Functional imaging data were analyzed using Nipype, a Python-based data processing framework that incorporates several neuroimaging data analysis packages (Gorgolewski et al., 2011). Standard functional image preprocessing (realignment, smoothing with 6-mm kernel, coregistration to structural) and analysis were done using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>). Advanced Normalization Tools (ANTS) (Avants et al., 2009) was used for warping functional data into MNI space.

First-level analysis was performed with a general linear model (GLM) with regressors for each of the four trial types (fearful, happy,

neutral faces and objects). Additional regressors accounted for head movement (3 translation, 3 rotation parameters) and artifact/outlier scans (see Section 2.5.2: Head motion and artifact detection). Each outlier scan was represented by a single regressor in the GLM, with a 1 for the outlier time point and 0 elsewhere. Contrast images from the first-level analysis were spatially normalized to a pediatric brain template in MNI space (Ghosh et al., 2010) using ANTS. Normalized contrast images were entered into a group-level analysis in SPM8 using a random-effects model. We examined two contrasts of interest: Fearful Faces > Neutral Faces and Happy Faces > Neutral Faces. All reported clusters survived the threshold of $p < .05$, corrected using a false discovery rate (FDR) error correction for multiple comparisons implemented in SPM8, with a voxel level significance of $p < .05$. Because the two groups differed in CBCL total scores, we repeated the between-group analysis with CBCL total score as a covariate, to test if group differences in brain activations could be accounted for by differences in CBCL scores.

2.5.1. Amygdala ROI analysis

To further examine activations in the amygdala under different facial expression conditions, we defined an amygdala ROI from bilateral amygdala masks in WFU pickatlas tool (Maldjian et al., 2003). Activations from the amygdala ROI were extracted for the fearful face, happy face, neutral face, and object conditions separately for each participant.

2.5.2. Head motion and artifact detection

Participant head motion during the functional scans did not differ between the at-risk group (mean = $.27 \text{ mm} \pm .19$) and controls (mean = $.30 \text{ mm} \pm .14$; $p = .5$). We identified problematic time points during the scan using Artifact Detection Tools (ART, http://www.nitrc.org/projects/artifact_detect/). Specifically, an image was defined as an outlier (artifact) image if the average intensity deviated more than 3 SD from the mean intensity in the session, or composite head movement (combining translation and rotation) exceeded 1 mm from the previous image.

The number of outlier images did not differ between at-risk (mean = 10.2 ± 11.6) and control (mean = 8.9 ± 7.3 ; $p = .7$) participants. Outlier images were modeled in the first level general linear model (GLM).

2.6. Structural analysis

Anatomical images were processed in FreeSurfer v5.0 (Dale et al., 1999). We focused on volumes of the amygdala and hippocampus. Each participant's anatomical image was processed using an automated segmentation and probabilistic region-of-interest (ROI) labeling technique (FreeSurfer, <http://surfer.nmr.mgh.harvard.edu>). Relative amygdala volume and hippocampal volume were calculated by dividing raw amygdala or hippocampal volume by total cranial volume in each participant.

3. Results

3.1. Participant demographics (Table 1)

Children in the at-risk and control groups did not differ significantly in age, gender distribution, or IQ. The two groups did not differ significantly for total CDI scores or on any CDI subscale (Negative Mood, Interpersonal Problems, Ineffectiveness, Anhedonia, and Negative Self Esteem, $ps > .2$). Although the at-risk group had significantly higher CBCL total scores compared to the control group, none of the children had clinical-range CBCL total scores. Because total scores differed between groups, we covaried CBCL total scores in further analyses to determine whether they affected the results.

Table 1

Subject demographic and clinical information. Mean \pm SD where appropriate.

	Controls (N = 14)	At-risk (N = 36)	Between-group test p-value
Age	11.6 \pm 2.14	11.1 \pm 1.35	.38
Gender	6 F, 8 M	18 F, 17 M	.75
IQ (KBIT)	112.3 \pm 11.6	117.6 \pm 13.0	.22
Mother affected	0	24	–
Father affected	0	14	–
Both parents affected	0	4	–
Life time depression	0	2	–
CBCL total	38.3 \pm 10.5	47.6 \pm 11.6	.02
CBCL internal	43.2 \pm 7.9	48.6 \pm 11.5	.17
CBCL external	41.8 \pm 9.8	47.1 \pm 9.9	.13
CBCL anxiety problems	51.4 \pm 2.5	54.9 \pm 6.7	.06
CDI total	3.9 \pm 3.1	5.6 \pm 4.4	.13
ERC lability/negativity	21.6 \pm 6.4	24.8 \pm 5.5	.06
ERC emotion regulation	28.0 \pm 4.1	27.6 \pm 3.2	.63

F, female; M, male; CBCL, Child Behavior Checklist; CDI, Child Depression Inventory; ERC, Emotion Regulation Checklist.

3.2. Face-match task behavior

Both groups performed near ceiling on the face-match task Table 2. The groups did not differ in reaction times in any of the test conditions ($ps > .2$), or accuracy for the happy face, neutral face, and objects conditions ($ps > .3$). Accuracy for the fearful faces was lower in the control than the at-risk group ($t(48) = 2.24$, $p = .03$), although accuracy for both groups was above 97%.

3.3. fMRI results

3.3.1. Fearful faces > neutral faces (Table 3)

Compared to the control group, the at-risk group showed increased activation in widespread regions with a right anterior medial temporal lobe cluster including the amygdala, superior temporal gyrus, posterior cingulate cortex and precuneus, middle prefrontal cortex, and superior parietal lobule when processing fearful faces compared to neutral faces (Fig. 1). These activation differences between at-risk and control groups remained when the CBCL total score was included as a covariate. When the two at-risk participants with previous history of depression and the two at-risk participants with clinical-range CBCL internalizing scores were excluded, the group difference pattern remains highly similar (Table S1).

Within-group analysis revealed that the at-risk group exhibited activations in bilateral amygdala, fusiform gyrus, superior temporal gyrus, posterior cingulate gyrus, and middle frontal gyrus when processing fearful faces compared to neutral faces (Fig. 2A). The control group exhibited activations in the superior temporal gyrus, inferior and middle frontal gyrus (Fig. 2B). The total number of active voxels for each group for fearful versus neutral faces is shown in Fig. 3 (left 2 bars).

3.3.2. Happy faces > neutral faces (Table 4)

Compared to the at-risk group, the control group showed greater activations in anterior cingulate gyrus, superior frontal gyrus and supramarginal gyrus when processing happy faces compared to neutral faces (Fig. 4). These differences remained when the CBCL total score was

Table 2

Mean accuracy (percent correct) and reaction time (ms) from the fMRI task.

		Happy faces	Fearful faces	Neutral faces	Objects
Accuracy	At-risk	.979	.987	.980	.996
	Controls	.975	.972	.978	1.00
Reaction time (ms)	At-risk	1098	1143	1166	837
	Controls	1047	1080	1086	798

Table 3

Group results for fearful faces > neutral faces. Coordinates (x, y, z) are based on MNI brain (Montreal Neurologic Institute). BA, Brodmann area. p-Value, FDR-corrected cluster-value p-value.

	BA	x, y, z	t	p-Value
<i>Fearful faces > neutral faces</i>				
At-risk > Controls				
Anterior MTL/amygdala		12, -5, -17	3.58	<.001
Superior temporal gyrus	22	67, 12, 9	3.88	<.001
Precuneus/posterior cingulate	19/30	23, -80, 36	3.65	<.001
Middle frontal gyrus	10/46	45, 60, 5	3.39	.002
Superior parietal lobule	7/40	26, -58, 56	2.75	<.001
Cerebellum		54, -51, -42	3.51	<.001
Controls > At-risk				
Temporopolar area/uncus	38	30, 1-48	3.85	.001
At-risk				
Superior temporal gyrus	41	50, -40, 10	4.85	<.001
L amygdala		-26, -2, -20	3.43	
R amygdala		29, -2, -15	3.86	
R fusiform gyrus	37	35, -32, 20	3.62	
Middle frontal gyrus	46/9	45, 24, 22	3.38	
Posterior cingulate	30	25, -52, -4	3.30	
Controls				
Superior temporal gyrus	22	60, -43, 20	5.97	<.001
Inferior frontal gyrus		26, 29, -28	4.43	<.001
Middle frontal gyrus	6/46/9	39, 18, 26	4.08	<.001

included as a covariate. When the two at-risk participants with previous depression and the two at-risk participants with clinical-range CBCL internalizing scores were excluded, the group difference pattern remains similar with slightly reduced statistical significance (Table S2).

Within-group analysis revealed that the at-risk group only exhibited activations in a left superior temporal gyrus cluster, extending into the amygdala when processing happy faces compared to neutral faces (Fig. 5A). The control group showed widespread activations in the superior temporal gyrus, supramarginal gyrus, posterior cingulate gyrus, middle frontal gyrus and insula (Fig. 5B). The total number of active voxels for each group for happy versus neutral faces is shown in Fig. 3 (right 2 bars).

3.3.3. Amygdala ROI analysis

In the bilateral amygdala ROI defined anatomically, at-risk children and controls showed opposite pattern of activation levels for fearful faces compared to neutral faces or objects (Fig. 6). The control group did not show any difference in activation for fearful faces compared to neutral or happy faces or objects ($p > .4$). In contrast, at-risk children showed greater activations for fearful faces compared to neutral faces ($t(35) = 2.54, p = .016$) and compared to objects ($t(35) = 3.07, p = .004$).

3.3.4. Amygdala activation correlation with clinical scores

We also examined the relationship between activations in the amygdala cluster from the between group test for fearful > neutral faces contrast and clinical scores. Measures of depressed symptoms (total CDI, total CBCL, CBCL affective problems score, and ERC scales) did not correlate with activations from the amygdala (all $p > .2$). Similarly, the CBCL anxiety problems score did not correlate with activations from the amygdala cluster ($p = .18$).

3.4. Structural analysis

Compared to the control group, the at-risk group had a smaller right amygdala volume (adjusted by total brain volume) ($t(53) = 3.05, p = .003$, Fig. 7). The left amygdala volume (adjusted) was marginally lower in the at-risk group compared to control group ($p = .06$). Hippocampus volumes did not differ between the at-risk and control groups ($p > .6$). Amygdala volume did not correlate with the clinical scores ($p > .16$). The group difference in amygdala volume remained after excluding the two at-risk children with previous depression and the two at-risk children with clinical-range CBCL internalizing scores (left: $t(48) = 3.15, p = .003$; right: $t(49) = 2.20, p = .03$).

4. Discussion

We found significantly different patterns of neural responses to fearful and happy faces in unaffected children at familial risk for major depression relative to children without such familial risk. Specifically, the at-risk children exhibited *hyperactivation* of the amygdala and multiple cortical regions to fearful compared to neutral faces, and *hypoactivation* in multiple cortical regions to happy compared to neutral faces. The atypical amygdala activations, previously found in adults with major depression, in unaffected at-risk children supports the hypothesis that they may not represent the state of depression but rather represent trait neurobiological underpinnings of risk for major depression in the young, but these group differences extended far beyond the amygdala.

While the present findings about altered activations for emotional facial expressions in unaffected children at familial risk for major depression are in noteworthy accord with a prior study (Monk et al., 2008), our study extends this observation in several ways. First, the present study involved younger children (mean age 11 vs. 14) and therefore likely includes more children who will progress to major depression (Biederman et al., 2007; Hirshfeld-Becker et al., 2012). Second, the prior study found differential amygdala activation only during passive viewing of faces (when attention to the stimuli cannot be validated behaviorally) and not during active tasks. Here, we validated each child's perception and attention to the stimuli through their behavioral accuracy and found the activation differences. Third, the prior study

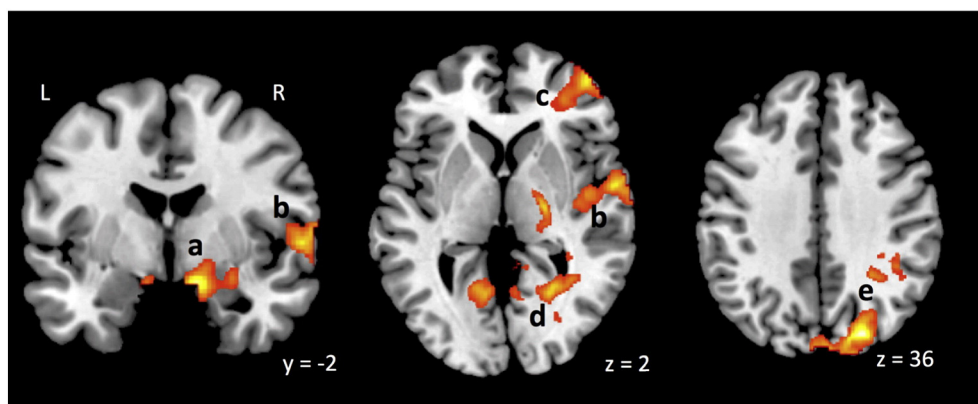


Fig. 1. Brain areas with higher activations for fearful faces > neutral faces in the at-risk group compared to the control group. a, Amygdala; b, superior temporal gyrus; c, anterior prefrontal cortex (BA10); d, posterior cingulate cortex; e, precuneus. Results are presented in neurological convention in all figures (left side of the brain is on the left side of the image).

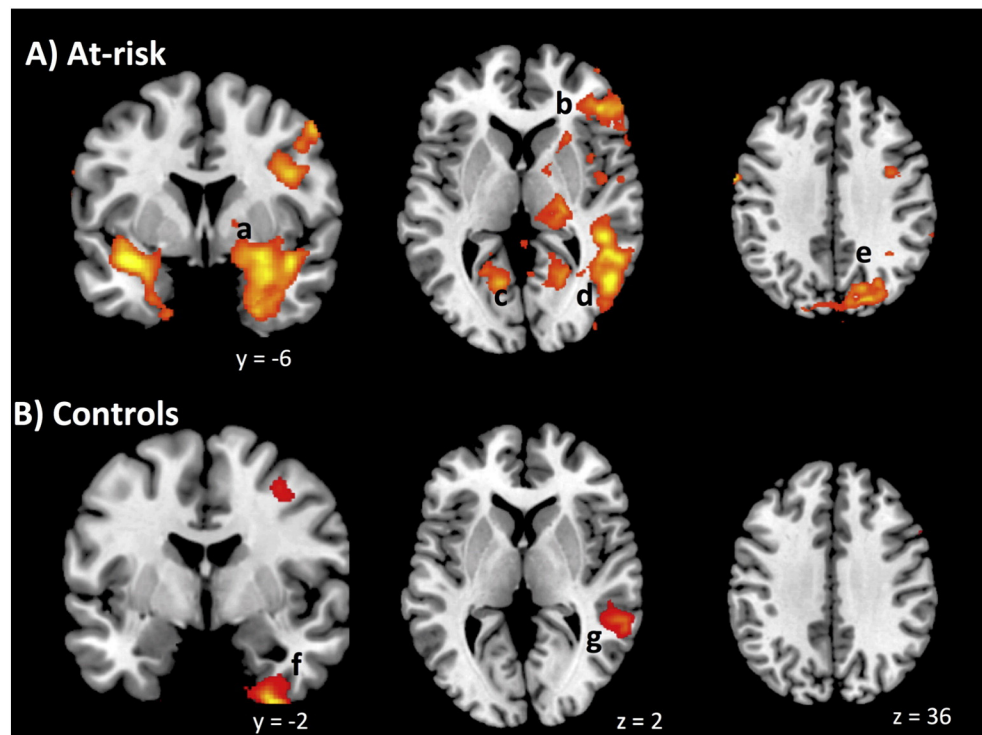


Fig. 2. Brain areas with higher activations for fearful faces compared to neutral faces within each group. A) At-risk group, B) control group. a, Amygdala; b, middle frontal gyrus; c, posterior cingulate cortex; d, superior temporal gyrus; e, precuneus; f, inferior temporal gyrus; g, superior temporal gyrus.

only examined activations in the amygdala and nucleus accumbens as a priori ROIs, leaving it unknown as to whether any other brain regions, including the entire neocortex, were functionally different in at-risk children. Indeed, we found that both the hyperactivations for fearful faces and hypoactivations for happy faces extended to large neocortical regions which have shown abnormal activations in depressed adult and adolescent patients during emotional face processing, such as anterior cingulate cortex (Zhong et al., 2011), posterior cingulate cortex (Fu et al., 2004), superior frontal gyrus (Gotlib et al., 2005), ventral lateral prefrontal cortex (BA10/47) (Keedwell et al., 2005), and superior/middle temporal gyrus (Hall et al., 2014; Suslow, 2010). Our findings

provide evidence that abnormalities in these neocortical regions pre-date the onset of major depression and might reflect neurobiological traits that predispose individuals to major depression.

For children at familial risk for major depression, there is a noteworthy convergence between the pattern of (1) attentional biases to faces in behavioral studies and (2) brain activations in response to faces. Behaviorally, at-risk children showed greater attention to negative facial expressions and lesser attention to positive facial expressions relative to control children (Gibb et al., 2009; Joormann et al., 2007; Kujawa et al., 2011). Neurally, at-risk children also showed greater activation for negative facial expressions and lesser activation for positive facial expressions relative to control children (present study; Monk et al., 2008). It would be expected that greater and lesser psychological attention to facial expressions would reflect, respectively, greater and lesser neural processing of specific emotional facial expressions. A

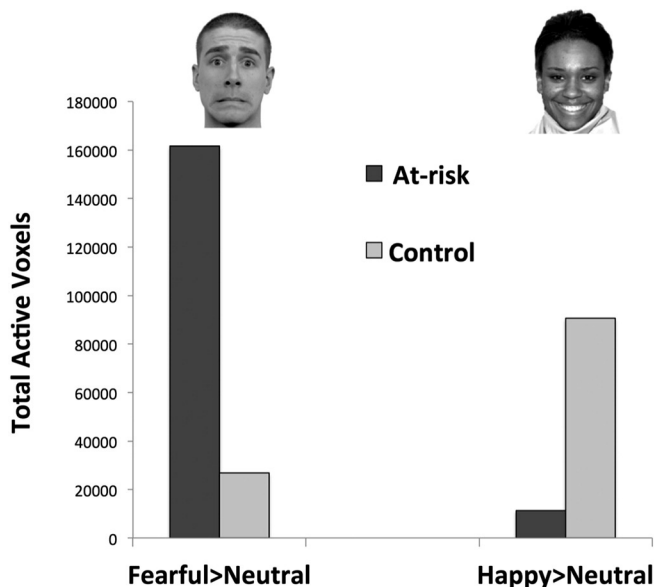


Fig. 3. Total numbers of active voxels for the fearful faces > neutral faces and happy faces > neutral faces contrasts in each group.

Table 4

Group results for happy faces > neutral faces. Coordinates (x, y, z) are based on MNI brain (Montreal Neurologic Institute). BA, Brodmann area. p-Value, FDR-corrected cluster-value p-value.

	BA	x, y, z	t	p-Value
<i>Happy faces > neutral faces</i>				
<i>Controls > at-risk</i>				
Superior frontal gyrus	8/6/9	13, 24, 66	2.99	<.001
Anterior cingulate gyrus	32/9	11, 32, 21	2.56	
Supramarginal gyrus	39/40	−53, −53, 32	2.95	.023
<i>Controls > at-risk</i>				
None				
<i>At-risk</i>				
Superior temporal gyrus	38	−43, 3, −18	4.85	<.001
<i>Controls</i>				
Anterior cingulate gyrus	32/9/8	11, 32, 21	3.75	<.001
Superior temporal gyrus	22/21	−48, −26, −22	4.24	<.001
L supramarginal gyrus	40/22	−56, −55, 19	3.62	<.001
R supramarginal gyrus	40/22	58, −54, 18	3.26	<.001
Posterior cingulate gyrus	31	4, −61, 32	3.21	.001
Middle frontal gyrus	46/45	−55, 7, 26	3.76	.004
Insula	13	38, 12, −17	3.43	.004

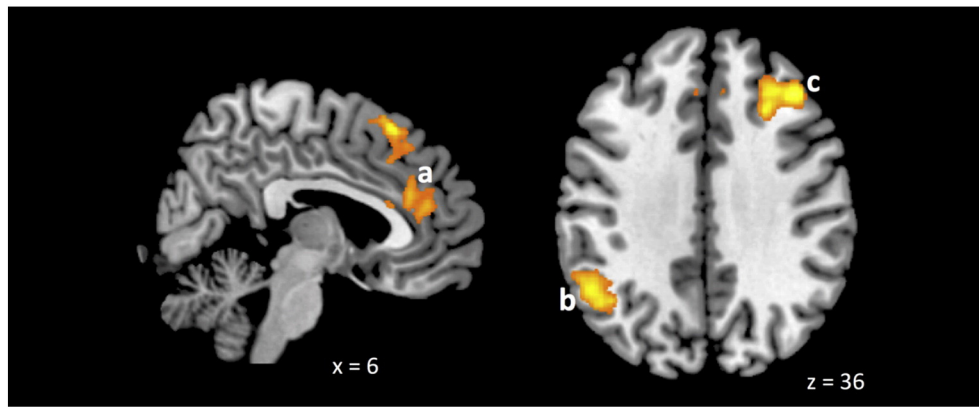


Fig. 4. Brain areas with higher activations for happy faces > neutral faces in control group compared to the at-risk group. a, Anterior cingulate cortex; b, supramarginal gyrus; c, superior prefrontal gyrus.

future study may directly relate these behavioral and neural biases in emotion processing.

At-risk children in the present study showed smaller amygdala volume compared to controls. This finding suggests that reduced amygdala volume previously reported in neuroimaging studies of adult major depression (Hamilton et al., 2008) may represent a trait-marker of risk for major depression that predates its onset. This interpretation is consistent with previous findings showing that patients with remitted and current major depression did not differ in amygdala volume (Caetano et al., 2004).

Although it is well established that the amygdala is activated by fearful faces in adults (e.g., Breiter et al., 1996; Morris et al., 1996), and appears necessary for adult recognition of fearful facial expressions (Adolphs et al., 1995), the development of specific amygdala activation

for fearful faces appears to occur over an extended age range. A specialized response of the amygdala to fearful expressions is not evident through at least age 12 years (Pagliaccio et al., 2013; Thomas et al., 2001; Tottenham et al., 2011). In this context, at-risk children appear to have an accelerated development of the selective amygdala response to fearful faces.

This finding converges with the observation that children who were exposed to early life stress had elevated amygdala activations to fearful faces whereas a control group did not show differential responses for fearful faces and neutral faces (Tottenham et al., 2011). It is unknown whether risk for major depression and elevated early life stress share a mechanism by which there is accelerated development of amygdala specialization for response to fearful facial expressions. That the present finding was not simply accounted for by elevated anxiety in the at-risk

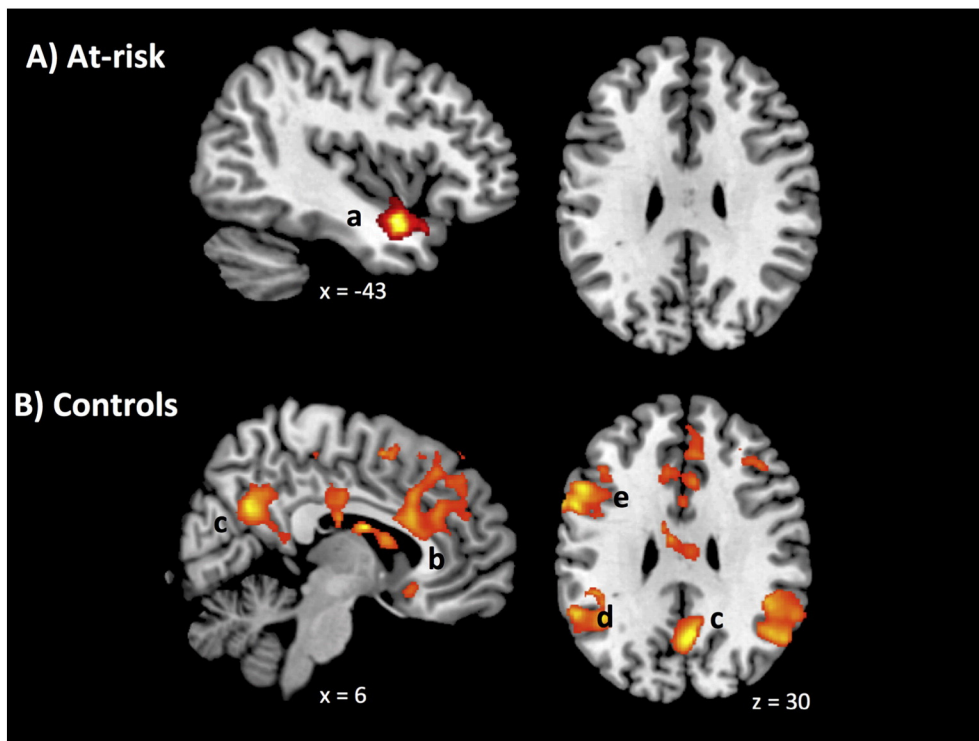


Fig. 5. Brain areas with higher activations for happy faces compared to neutral faces within each group. A) At-risk group, B) control group. a, Superior temporal gyrus; b, anterior cingulate cortex; c, posterior cingulate cortex; d, supramarginal gyrus; e, middle prefrontal gyrus.

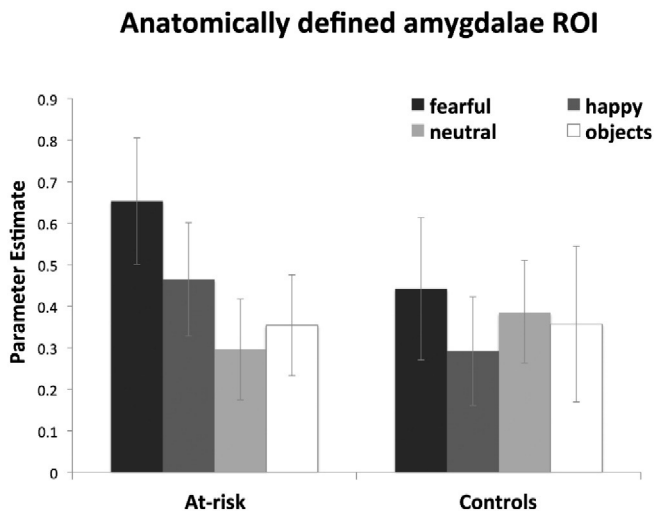


Fig. 6. Activations in anatomically defined amygdala ROI (bilateral) for each trial type. Bars represent mean activations for each trial type within each group. Error bars represent standard errors of the mean.

children is suggested by the fact that the amygdala activation to fearful faces was not significantly associated with CBCL-measured anxiety problems.

A complete interpretation of these functional and structural brain differences in at-risk children will require additional research. First, because a parental history of major depression more than triples the risk for major depression, and because the pattern of brain differences is similar to that seen in adults with major depression (who would exhibit both the state and trait of major depression), these brain differences are presumed to indicate vulnerability to major depression. There is not, however, direct evidence whether the brain differences observed here could also indicate sources of brain resilience by which these at-risk children are avoiding major depression. Only a longitudinal study that follows at-risk children with both behavioral and brain measures can resolve this question. Scientifically and clinically, identification of brain mechanisms of vulnerability and resilience are both of great interest.

Second, the mechanisms of familial influences on brain function and structure related to major depression are unknown. One possible mechanism is shared intergenerational genetic influences on the development of brain structure and function. A second possibility is the environmental influence of a parent with depression upon the development of a child in the home. Both genetic and environmental influences, as

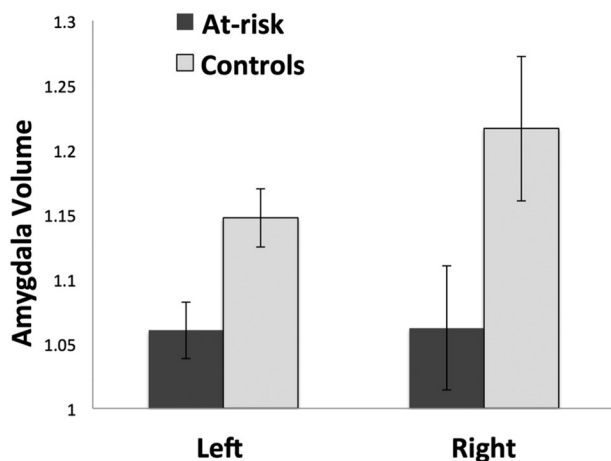


Fig. 7. Mean amygdala volume (adjusted for whole brain volume) in each group. Error bars represent standard errors of the mean.

well as their interactions, ought to be reflected in future neuroimaging studies examining brain structure and function.

The present study had important strengths and limitations. Parents and offspring were carefully characterized and comprehensively assessed with structured diagnostic interview. The findings were well aligned with neuroimaging studies of adult major depression and behavioral studies of children at familial risk for major depression. Some limitations were operant as well. Although levels of current anxiety did not correlate with brain activations in the children, parents were not assessed for anxiety disorders and other disorders that frequently comorbid with major depression, such as ADHD (Meinzer et al., 2014; McIntyre et al., 2010; Dobson, 1985). Similar to other studies of children with a parent with documented depression (Joormann et al., 2007; Mannie et al., 2011; Monk et al., 2008), such frequent comorbidities were not defined as an exclusion criterion. Conversely, current research approaches, such as the Research Domain Criteria initiative of the NIMH (Morris and Cuthbert, 2012) suggest that such comorbidities are a natural part of psychiatric disorders with possible common neural and genetic underpinnings, rather than impure versions of pure taxonomic diagnoses. Also, because the sample was largely Caucasian, findings may not generalize to other ethnic groups. Future studies ought to more fully evaluate the role of comorbid parental disorders of major depression, such as anxiety disorders and ADHD, in accounting for these findings and expand the study population to more diverse ethnic groups.

Despite these considerations, our findings showing that unaffected at-risk children exhibited patterns of atypical amygdala activations, previously found in adults with major depression, support the hypothesis that they represent trait neurobiological underpinnings of risk for major depression in the young. Further, differences between at-risk children and controls extend to activations associated with both fearful and happy facial expressions, and in many neocortical regions. If confirmed in future studies, this knowledge could promote the development of preventive and early interventions aimed at helping children avoid the development of major depression. Longitudinal follow-up studies of at-risk children could help determine whether these brain differences reported here could improve the identification of children who will actually develop major depression or other major psychiatric disorders.

Contributors

DHB, OD, AB and JDEG were responsible for the study concept and design. XJC, DHB, JL, JS, EK, TK and CDLA were responsible for data collection. XJC, JS and SWG performed the data analysis. XJC, DHB and JDEG drafted the manuscript. MU and JB provided critical revision of the manuscript for important intellectual content. All authors critically reviewed the content and approved the final version for publication.

Conflicts of interest

The authors report no conflicts of interest. Dr. Joseph Biederman is currently receiving research support from the following sources: The Department of Defense, AACAP, Alcobra, Forest Research Institute, Ironshore, Lundbeck, Magceutics Inc., Merck, PamLab, Pfizer, Shire Pharmaceuticals Inc., SPRITES, Sunovion, Vaya Pharma/Enzymotec, and NIH. In 2014, Dr. Joseph Biederman received honoraria from the MGH Psychiatry Academy for tuition-funded CME courses. He has a US Patent Application pending (Provisional Number #61/233,686) through MGH corporate licensing, on a method to prevent stimulant abuse. Dr. Biederman received departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Ingenix, Prophase, Shire, Bracket Global, Sunovion, and Theravance; these royalties were paid to the Department of Psychiatry at MGH.

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Appendix A. Supplementary data

Supplementary material for this article can be found online at <http://dx.doi.org/10.1016/j.nicl.2015.05.004>.

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